

REMARKS

Applicants acknowledge the cancellation of claims 5-6 as an election without traverse. Applicants retain their right to file a divisional application thereon.

Applicants have made changes in the claims and have added two new claims. Applicants believe that no new matter has been added to the claims. The two new claims have been copied from claim 3, with changes in dependency. In several of the claims, the phrase "hemorrhagic or thrombotic" has been added; support for this is a definition found on page 1, lines 18-19. In claims 3, 18 and 19, the term "pig" has been replaced with "mammalian;" pigs are well known to be mammals; plus "mammalian" is supported on pages 6-7, the bridging paragraph. To claim 14 was added the phrase "of the brain or to cerebral spinal fluid;" on pages 7 and 8, the bridging paragraph, the injection was performed into the cisternal space - part of the cerebrospinal fluid. The term "cisternae" already appears in claim 16.

As requested, new, corrected declarations of inventorship have been prepared, signed by Applicants and are enclosed with this amendment. Applicants have signed declarations including all the priorities of this application, including two provisional applications (60/131,230 filed April 27, 1999, and 60/144,785 filed July 20, 1999). Also enclosed is a corrected filing receipt showing these two additional priority dates, which were overlooked when the 35 USC Section 371 application was processed.

In response to the claim 15 objection, Applicants have inserted the word "into" before "a location."

35 USC § 102 Rejections

Claims 1, 3, 4, 7-12, 14-15 and 17 were rejected as being anticipated by Simm (Berlin On-line, March 3, 1999). Applicants herein provide grounds to antedate this reference. As mentioned above, Applicants have had the erroneously omitted priority data added to the corrected filing receipt. The earliest provisional priority date now established is April 27, 1999. Also enclosed is a separate Rule 1.131 declaration by all the inventors stating that the invention was reduced to practice on or before July 1, 1998, when the University of Pittsburgh Medical Center announced the first transplant. This invention date is less than one year before the first

filing date of April 27, 1999. This proof of invention antedates the March 3, 1999, date of the Simm reference. In addition, the inventors continued to diligently reduce their invention to practice through additional human implantation and following all implanted patients to the filing date.

Although Applicants supplied the Simm reference, they have not represented the Simm reference as prior art because a disclaimer appeared in the November 12, 2002, the Information Disclosure Statement (page 1) that cites Simm. The disclaimer is as follows: "This Information Disclosure Statement ... is not to be construed as a representation that ... any one or more of these items constitutes prior art."

Applicants respectfully request that this ground for rejection be withdrawn.

Claim 17 was considered anticipated by Canadian Patent publication CA2213780 (the '780 publication) which discusses replacing nerves in the CNS lost to neurodegenerative disease, trauma, ischemia or poisoning by administering neuronal cells.

In response, Applicants offer the following comments. At page 8, lines 8-9, the reference says that the cells "can be passaged and differentiated into cell types of the CNS, including astrocytes, oligodendrocytes, and *dopaminergic* neurons (emphasis added)." The same three cell types are again the only ones mentioned in line 12 on the same page. Later on the same page, the stem cells were differentiated into neurons, but the only type of neuron mentioned is dopaminergic. Moreover, when the precursor cells were differentiated, only significant numbers of dopaminergic neurons were found in all differentiated cultures of "olfballs." (page 14, lines 17-20) The '780 publication defined olfballs as floating spheres derived from olfactory stem cells. In addition, the '780 publication stated on page 18, lines 22-24, that because the olfballs were layered on one another where the olfball had attached, it was not possible to count the number of cells expressing each marker. In other words, the inventors could not differentiate dopaminergic from other neurons. Suddenly, in their conclusions concerning Example 2, the inventors stated that GABAergic neurons were present, without mentioning how the cells were identified, which calls into question whether or not the cells indeed were GABAergic. While the title of Example 4 is "Precursor [neural stem] Cells Differentiate Into Neurons When Transplanted into Adult Brain," the example not only lacks enablement but was stated in the

present tense, which likely indicates that the experiments were never done and no experimental data existed to support the inventors' allegation. Subsequently, the '780 publication stated that differentiated olfballs were implanted into adult rats after the dopaminergic cells on the same side were destroyed. Again, the nerve cells were only reported to be TH neurons for Parkinson's Disease.

Hence, the '780 publication does not enable anticipation, because the publication does not disclose the broader differentiable cell types required for the treatment stroke treatment and neurodegenerative disorders. Test results were only reported for dopaminergic cells which would be useful in Parkinson's Disease, which is only one of many different neurodegenerative diseases. The publication only *proposes* other types of cells and disorders, but fails to provide any data supporting enablement therefor.

Furthermore, the reference states in Example 7, lines 13-15: "If olfactory-derived neural stem cells are to be used for autologous transplants for the treatment of neurodegenerative disorders *it is necessary to show that they can be generated from human nasal epithelium* (emphasis added)." This appears to be an admission of non-enablement for human cells. In spite of the stated need to show that human neural stem cells "can be obtained from human nasal epithelium," no experimental data were provided to show such a result, and thus there is no human enablement. All the experimental work was conducted only in rats and mice. In addition, even in those experimental models, no functional improvement after induced stroke or Parkinson's disease was demonstrated. Thus, it is questionable whether implantation into humans is enabled.

In the accompanying 1.131 declaration, paragraph 3, Applicants, who have broad and deep experience with such models, state that such models are commonly used but the experimental results are uncommonly verified in properly conducted and controlled human studies. That is why the first provisional application was not filed until the human pilot study yielded positive results in humans.

Therefore, while the '780 publication proposes use of neural stem cells in stroke, 1) the differentiated cells are only of limited types and unlikely to successfully treat stroke or other neurodegenerative diseases, except for Parkinson's Disease and related disorders of DOPA neurons; and 2) the positive (anatomically but not functional) animal results do not enable human treatment, especially since the '780 publication cautions that, "*it is necessary to show that they*

[human neural stem cells] *can be generated from human nasal epithelium* (emphasis added)."

In conclusion, Applicants request that this ground for rejection be withdrawn.

35 U.S.C. §103

To establish a *prima facie* case of obviousness under 35 U.S.C. §103, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the cited prior art references must teach or suggest all of the claim limitations. Furthermore, the suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not based upon the Applicants' disclosure. A failure to meet any one of these criteria is a failure to establish a *prima facie* case of obviousness. MPEP §2143.

The first Section 103 rejection stated that claims 1-4 were unpatentable over U.S. Patent No. 5,851, 832 (Weiss *et al*, issued 12/22/98 and filed 6/7/95) (the '832 patent) in view of Sanberg *et al* (Soc Neurosci 140.9, 1997, 23(1-2): 346) and further in view of Grabowski *et al* (Exp Neurol 1994, 127(1): 126-36, Abstract only).

The Office Action described the '832 patent as disclosing a method for the treatment of neurodegenerative disease comprised of administration to a mammal of mammalian neural stem cell progeny that had been induced to differentiate into neurons and/or glia (column 11, lines 13-17). The reference mentions a myriad of neurodegenerative disorders, including stroke, and even a plethora of CNS disorders (*e g*, depression, epilepsy and schizophrenia) in the Background section. The Detailed Description briefly describes prophetic implantation of neural progenitor cells into a patient having undergone a computed tomography scan to determine the coordinates of the region to receive the transplant, forming a burr hole, and injecting the cells.

Viewing the reference as a whole, one can see that both rodent (Examples 1-8) and primate cells were processed to produce neurospheres and their progenies, including nerve cells and other nervous tissue cells. In addition, some rodent models were implanted with either embryonic or adult-derived nervous tissue. Additionally, there is a hypothetical example of a patient with non-specified "neurodegenerative disease" receiving fetal cells (Example 14). Examples 16 and 17

also are hypothetical examples of the treatment of the demyelinating diseases neuromyelitis optica and Pelizaeus-Merzbacher disease. In addition, Example 18 is a hypothetical example of administration into a human patient as described in Example 14. These are all hypothetical examples.

As with the '780 publication, there is no example of successful transplantation into humans, just rodent models which do not have a reasonable expectation of success in providing therapeutic benefit in humans. Thus, although the '832 patent alleges human treatment of neurodegenerative disorders, it provides no details such as are claimed by Applicants.

The Office Action describes Sanberg *et al* as teaching successful implantation of hNT cells to ischemic rats, producing dose-dependent behavioral recovery. Rats receiving the highest dose (40,000 hNT cells) showed the highest rate of recovery.

In response, Applicants point out that this also is an animal model. As mentioned earlier, success in this animal model does not provide a reasonable expectation of success in humans.

The Office Action describes Grabowski *et al* as teaching the implantation of fetal cortical tissue into the rat stroke model at 5-7 days, 3 weeks and 8 weeks. Rats fared better with implantation 3 weeks and 8 weeks after stroke. This was considered to render unpatentable the dependent claim to at least three months. Since there was no three-month group, this is questionable.

In response, Applicants question how rat model used by Grabowski *et al* is applicable to humans. First, Grabowski only teaches the implantation of fetal rat neocortex obtained from the same location as the recipient had its stroke induced. Such a source of cells is of questionable applicability for the cell types mentioned in claim 3. Secondly, this is a rat model which does not have a reasonable expectation of success in human therapy.

Given the lack of teachings and or suggestion of combination to produce all the elements of the claims, Applicants do not believe that a *prima facie* case of obviousness has been made. Applicants, who are among those highly skilled in the art, indicate that there is no reasonable expectation of success. The references only cover rodent models which do not provide the essential teachings needed to support the reasonable expectation of success. None cover or supply the missing teaching of humans. Therefore, Applicants request that this rejection be withdrawn.

In a second Section 103 rejection, the Office Action rejected claims 7-17 under 35 USC 103(a) as unpatentable over Sanberg and Borlongan (Soc Neurosci Abstr 232.9, 1996, 22 (1-3):578) in view of the Weiss '832 patent and further in view of Uchida *et al* (Exp Neurol 1995, 132: 194-208). Noting that the claims are drawn to a method of improving speech, motor performance, cognition, and sensory function in a person with brain damage due to stroke, the Office Action also stated that these claims cover replacement of nerves lost to neurodegenerative disease such as trauma, ischemia, or poisoning, by administering a sterile composition of a sufficient number of neuronal cells into the damaged area.

Next the Office Action stated that Sanberg and Borlongan teach the transplantation of human-origin hNT cells into rats which had been subjected to ischemic embolism and occlusion of the middle cerebral artery one month earlier. The rats treated with hNT cells or rat fetal striatal tissue had improvements in the motor and cognitive deficits associated with ischemia. The Office Action acknowledged that there is no animal model for speech, but several brain regions, including the cognitive area are involved in speech.

In response, Applicants note that the rat model of stroke does not have a reasonable expectation of success in human treatment. Therefore, this reference does not contribute to rendering the cited claims obvious.

The Office Action next cited the '832 patent for disclosing a method of treating neurodegenerative diseases by administering neural stem cell progeny from mice to mice models.

In response, Applicants note that the human uses were only hypothetical. Thus, this patent also is limited to use in rodent models, which do not have a reasonable expectation of success in humans.

The Office Action next cited the Uchida *et al* reference for its teaching that transplanted neuronal cells survive greater than one year in an adult host and that the transplanted cells migrated some distance from the implantation location.

In response, the Applicants note that Uchida *et al* only covers transgenic mice with β -gal-positive brain cells from donor mice to mice of the exact same inbred line. The teaching in Uchida *et al* is thus limited to the implantation of cells of the exact same genetic make up as the recipient. Moreover, the donated tissue was mesencephalic neural plate, which is of questionable

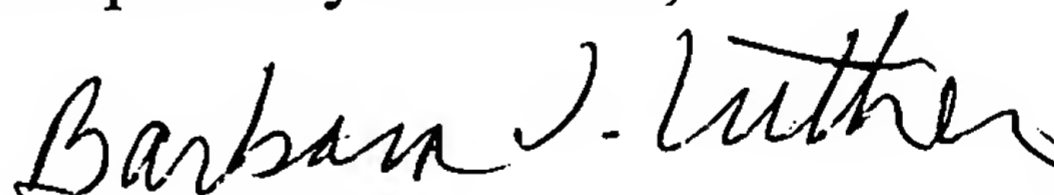
applicability to the cells types mentioned in claim 3. In response to the Office Action proposal that cells migrated away from the explanted tissue mass, Applicants observe that Uchida *et al* also state (in the next to last paragraph) "it cannot be ruled out that the distant cells were *deposited at their sites during implantation* (emphasis added)." This is consistent with the carefully wording of the Abstract: "Some β -gal-positive cells were observed to *lie* up to 230 μ m away from the main graft mass... (emphasis added)." In addition, the only animals tested were mice, which do not have a reasonable expectation of success in humans.

Applicants believe that a *prima facie* case of obviousness has not been made. There is no suggestion in the referenced prior art to modify the references to produce the Applicants' claims. As stated above, there is no reasonable expectation of success found in the cited prior art. Applicants respectfully request that this ground for rejection be withdrawn.

CONCLUSION

In light of the above claim changes and arguments, Applicants believe that a Notice of Allowance may be issued forthwith. If there are any issues which can be resolved by telephone conference or an Examiner's Amendment, the Examiner is invited to call or otherwise contact the undersigned attorney at 480-275-8302.

Respectfully submitted,



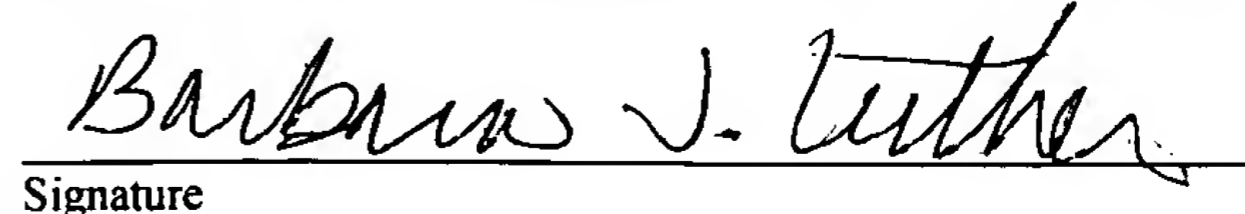
Date June 28, 2006 By _____
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Enclosures: New Declarations of Inventorship, Corrected Filing Receipt, 1.131 Declarations

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being transmitted by Express Mail No. ED643288798US and addressed to Box Amendment, Commissioner for Patents, P.O.Box 1450, Alexandria, VA 22313-1450 on this 28th day of June, 2006.

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Signature